

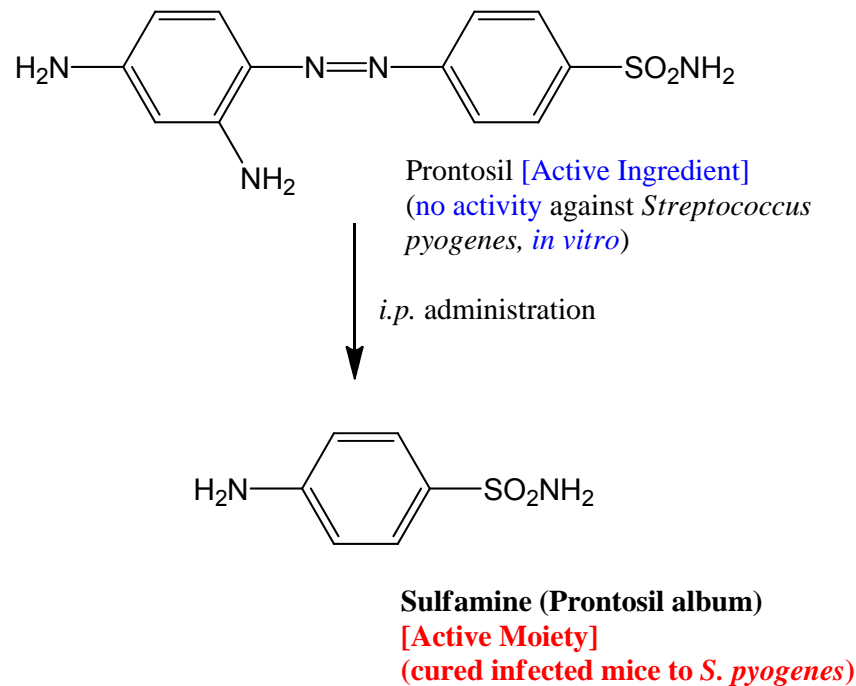
Active Ingredient-Active Moiety Relationship in SPL

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What is an active moiety?

- The part of a drug that makes the drug work the way it does (therapeutic effect).



- Many different drug products may be marketed with the same active moiety.

Active Moieties

[21CFR314.108(a), 316.3(b)2, 516.3(b)]

1. Molecules (excluding appendix portions of ester, salt)

- Intact molecule

Acetaminophen, Aspirin, Levodopa, ...

- Salt

Pantothenic Acid for Calcium Pantothenate

- Ester (prodrug)

Moexiprilat for Moexipril Hydrachloride

- “Exception”

Homosalate [ester of salicylic acid]

⇒ **Salicylic Acid is not AM**

Active Moieties (cont.)

[21CFR314.108(a), 316.3(b)2, 516.3(b)]

2. Ion (no salt)

- Iodide Ion (I^-) for Potassium Iodide (KI)
- “Exception”

Sodium Chloride (NaCl)

- ➔ 1) Sodium Chloride (NaCl) : to maintain isotonic conditions
- ➔ 2) Sodium Cation (Na^+) : to treat Hyponatremia

3. Noncovalent derivatives of the molecule (complex, chelate, clathrate)→ case-by-case; usually, choose real active moieties

- Ferric Cation for Iron Dextran

Other Active Moieties

In many cases Active Moieties are the same as Active Ingredients.

- Plant materials
 - Common name (Herbs of Commerce)
 - Latin binominal name + plant part
- Microorganisms
 - Latin binominal name
- Biologics (Protein, Enzyme, Allergen, Vaccine, Antibody, etc.)
- Homeopathic ingredients (Plant, Animal, Bacteria, Natural toxin, etc.)

Active Ingredient-Active Moiety relations review

- CVM Ingredient tables (three tables)
- Drugs@FDA Data File (1/4/2012 updated)
 - Find Ingredients without AM and identify AM
- NDC Directory files
 - Find Active Ingredients without AM and identify AM (867/5200 ingredients)
 - Old file (10/20/2011 final-update)
 - New file (1/3/2012 updated)

Review Scheme

Active Ingredients

(CVM, Drugs@FDA, NDC Directory files)



Ingredients are already in SPL Data file

(Active Ingredient-Active Moiety relations established)



YES

No further Action
at this moment

NO



Identify and Confirm Active Moieties

Some problems (1)

1. Active Moiety

a) Hydrus vs. Anhydrous

- USAN frequently does not indicate “hydration” status
 - Cefadroxil (monohydrate) → **Cefadroxil Anhydrous (Cefadroxil [INN], [JAN])**
 - Tacrolimus (monohydrate) → **Tacrolimus Anhydrous (Tacrolimus [INN])**
 - Cidofovir (dihydrate) → **Cidofovir Anhydrous (Cidofovir [INN])**

b) Prodrug

- Corresponding active (underivatised) molecule should be AM
 - Fosamprenavir Calcium → **Amprenavir** (dephosphorylated)
 - Hetacillin Potassium → **Ampicillin???**
 - Benazepril Hydrochloride → **Benazeprilat** (deesterified)

Some problems (2)

c) Mixture

Some Active Ingredients are mixture so as AM

- **Interferon Alpha-N3**
 - Interferon Alpha-2A, 2B, 2C,
- Neomycin Sulfate → **Neomycin**
 - Neomycins A, B, and C

d) Totally misidentified AM

- Zinc Oxide or Benzophenone for **Oxybenzone**
- 1,2-Dimyristoyl-*sn*-glycero-3-(phospho-*rac*-(1-glycerol)) (sodium salt) for **Sodium Chloride**
- 2-Ethylhexyl 4-phenylbenzophenone-2'-carboxylate for **Octinoxate**

e) Stereo Chemistry

- Alpha-tocopherol
 - D-form (N9PR3490H9)
 - D,L-form (7QWA1RIO01)
 - Unspecified (H4N855PNZ1)

Some problems (3)

2. Active Ingredient

.....**Nonproprietary drug nomenclature** is therefore intended primarily for physicians, pharmacists, and those in related health professions **concerned with the understanding of the drug's pharmacological and therapeutic properties.**

(“USAN Program” from Preface, USP Dictionary 47th Ed., 2011)

➔ Nonproprietary Name prevents confusion about **the identity of the active ingredient** among proprietary preparations containing the same substance.

Some problems (4)

2. Active Ingredient (cont.)

- a) Usually, “Nonproprietary Name” = “Active Ingredient Name”
- Abacavir Sulfate (Nonproprietary) → Abacavir Sulfate (Active Ingredient)
 - Daunorubicin Citrate (Nonproprietary) → Daunorubicin Citrate (Active Ingredient)
- b) In some cases, “Nonproprietary Name” ≠ “Active Ingredient Name”
- i. Mis-assigned Nonproprietary names
 - Cefoxitin (Nonproprietary) → **Cefoxitin Sodium** (Active Ingredient)
 - Magnesium Sulfate (Nonproprietary) → **Magnesium Sulfate Heptahydrate** (Active Ingredient)
 - ii. Mis-assigned Active Ingredient names
 - **Chlorphenilamine Polistirex** (Nonproprietary) → Chlorphenilamine Maleate (Active Ingredient)
 - iii. Synonyms
 - Glutathione Disulfide (Nonproprietary) → **Oxiglutatione** (Active Ingredient)
 - OnabotulinumtoxinA (Nonproprietary) → **Botulinum Toxin Type A** (Active Ingredient)

Example - Azithromycin

Substance Name	Substance UNII	Correct Substance Name	Correct Substance UNII	SPL AM	SPL AM UNII	Correct AM	Correct AM UNII	Basis of Strength	Correct BOS
AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN DIHYDRATE	5FD1131I7S	AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN	AZITHROMYCIN ANHYDROUS
AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN DIHYDRATE	5FD1131I7S	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M			AZITHROMYCIN	AZITHROMYCIN ANHYDROUS
AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN MONOHYDRATE	JTE4MNN1MD	AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN	AZITHROMYCIN ANHYDROUS
AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN HYDROGENCITRATE	T7I43X3J2A	AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN	AZITHROMYCIN ANHYDROUS
AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M			AZITHROMYCIN ANHYDROUS	
AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN	AZITHROMYCIN ANHYDROUS
AZITHROMYCIN	F94OW58Y8V			AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN ANHYDROUS	
AZITHROMYCIN ANHYDROUS	J2KLZ20U1M			AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN	AZITHROMYCIN ANHYDROUS
AZITHROMYCIN ANHYDROUS	J2KLZ20U1M			AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN ANHYDROUS	
AZITHROMYCIN DIHYDRATE	5FD1131I7S			AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN DIHYDRATE	
AZITHROMYCIN DIHYDRATE	5FD1131I7S			AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN	
AZITHROMYCIN MONOHYDRATE	JTE4MNN1MD			AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN	
AZITHROMYCIN MONOHYDRATE	JTE4MNN1MD			AZITHROMYCIN	F94OW58Y8V	AZITHROMYCIN ANHYDROUS	J2KLZ20U1M	AZITHROMYCIN MONOHYDRATE	

Next Step (~July, 2012)

- SPL Data file review (AI-AM-BOS Relations)
- Register missing substances in SRS/UNII
- Active Moiety Classification
- SRS-AM Data file review

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